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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,986	02/25/2004	Seiko Hirano	US-109	1388

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EXAMINER

GEBREYESUS, KAGNEW H

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/784,986

Applicant(s)

HIRANO ET AL.

Examiner

Kagnew H. Gebreyesus

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-4 and 11 is/are allowed.
- 6) ☒ Claim(s) 5-10, 12, 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

1. Applicant's response filed on November 14, 2005 to the Office Action mailed on September 14, 2005 is acknowledged.

Withdrawn - Claim Objections

1. Objection to claim 8 is withdrawn following amendment of the claim.

Withdraw - Claim Rejections - 35 USC § 101

Claims 1-5 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Following the amendments to the claims the rejection has been withdrawn.

Withdrawn - Claim Rejections - 35 USC § 112

1. Claim 6 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards the implication of the word "derived". This rejection has been withdrawn following the amendment.
2. Claim 6 and 8 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards the invention. The rejection has been withdrawn following applicant's amendments.

Maintained - Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5, 10 are indefinite for the recitation of "under stringent conditions" as the specification does not define what conditions constitute "stringent". The condition recited in the claim as it stands is a description of a wash condition following and not a stringent hybridization condition. For examination purposes the intent of the claim will be understood as such.

Withdrawn - Claim Rejections - 35 USC § 112

5. Claims 1-9 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Following the amendment to the claims this rejection has been withdrawn.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been withdrawn following applicant's amendment.

Withdrawn - Claim Rejections - 35 USC § 102

1. Claim 1 was rejected under 35 U.S.C. 102(b) as being anticipated by Sabo et. al. As presently amended the disclosure by Sabo et al does not read on this claim therefor the rejection has been withdrawn.
2. Claims 3, 5 and 6 were rejected under 35 U.S.C. 102(b) as being anticipated by Kukuchi et al. Following the claim amendment this rejection has been withdrawn.

Claim Rejections - 35 USC § 103

3. Applicants request for clarification as to which of the two Gunji et al reference(s) has been applied to the rejection under 35 U.S.C. 103(a).
4. Applicants argue:
5. "It is first unclear which Gunji reference the Examiner is relying upon, since the cited published US patent application is NOT the equivalent or a translation of the cited Japanese WO patent, as the Examiner seems to indicate in the cover sheet of the Office Action sent on September 14, 2005. The US published patent application claims priority to Japanese patent application D2001-177075, which is not claimed as a parent to the WO patent. Therefore, the US published patent application is not an equivalent to the WO patent. Therefore, since the Examiner appears to be applying the Gunji et al. as a secondary reference to Kukuchi et al this rejection will be addressed as if the Examiner is citing both the Gunji et al. PCT patent application (W02000/61723) and the US published patent application US2003/0124687) as secondary references to the primary Kukuchi et al. reference. If this interpretation of the Office action is incorrect clarification of the Office Action is respectfully requested".
6. Furthermore applicants argue :
"As stated above, Kikuchi et al. describes a lysine decarboxylase gene which is only 51% homologous with the nucleotide sequence of SEQ ID NO:3. The sequences are very dissimilar and hence one of ordinary skill in the art would not be expected to arrive at the inventive DNA sequence, the *Methylophilus* bacterium, and/or the disrupted gene resulting in suppression of lysine decarboxylase activity without undue experimentation.
Similar to the disclosure of U52003/0124687 the disclosure of the W000/61723 reference also fails to make up for the deficiency of Kikuchi et al. with respect to the subject matters of the pending claims, since W000/61723 only describes the use of *Methylophilus* bacteria for producing L-amino acids and discloses nothing of disrupting any gene for the purpose of

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suppressing lysine decarboxylase activity, nor mentions the lysine decarboxylase gene of any sequence. One of skill in the art would not be motivated to combine the teachings of these references since there is no indication that the gene of Kikuchi et al., which is very dissimilar as compared to the claimed gene would function in the *Methylophilus* ms does the inventive gene sequence of SEQ ID NO: 3.

7. Applicants argument regarding the use of reference US2003/0124687 A1 was carefully considered and found persuasive therefore this reference (US2003/0124687 A1) will not be applied in the rejection under 103(a) in view of applicants statement under 103(c). However claims 7- 9 and 12 and 13 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et. al. (US PAT 5,8276,98) and Gunji et al. (WO2000/61723).

Given that Gunji (WO2000/61723) references teaches a methanol assimilating bacterium namely *Methylophilus* bacterium and that it teaches methods of producing L-amino acids and specifically L-lysine using the same, WO2000/61723 can be applied together with Kikuchi et. al. (US PAT 5,8276,98).

8. The requirement for a rejection under The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applicant's argument with regards to the disruption of any gene for the purpose of suppressing lysine decarboxylase gene of any sequence was not found persuasive. As stated in the previous Office Action Kikuchi et al., teach a method of producing increased level of L-lysine by disrupting the L-lysine decarboxylase genes (*cadA* and *ldc*) in *E. coli* using a plurality

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of methods including substituting a normal polynucleotide in the genome of the bacterium by a modified polynucleotide or disrupting or polynucleotides using homologous recombination.

Disruption of L-lysine decarboxylase polynucleotide in this bacterium leads to accumulation of L-lysine by virtue of a decreased rate of L-lysine degradation. The *E. coli* is grown in liquid media containing glucose as the main carbon source and the L-lysine is collected from the culture. However Kikuchi et. al. do not use *Methylophilus* bacteria.

9. As stated in the previous Office Action applicant's inventions are drawn to a *Methylophilus* bacterium in which the lysine decarboxylase activity has been either reduced or eliminated or wherein the polynucleotide sequence encoding said enzyme is disrupted such that its expression is suppressed resulting in reduction or elimination of the enzyme activity followed by the use of such a bacteria for the production of L-lysine from a culture media containing methanol as the major carbon source and collecting the L-lysine from the culture.

Therefore the difference between the invention of the prior art and the invention of the instant application is the microorganism used to attain the objective. The difference between Kikuchi's inventions and the present invention is that applicants use a bacterium (*Methylophilus*) that utilizes a one carbon compound (methanol) as the major carbon source as opposed to *E. coli* which uses glucose (six carbons) as its major carbon source.

The level of ordinary skill in the art at the time the invention was made was adequately high enough to permit an ordinary person of skill in the art to isolate a gene such as *idc* or *cadA* and modify/disrupt the function any gene from any microorganism by various methods including homologous recombination, over-expression. One of ordinary skill in the art would have a

reasonable expectation of success since Kikuchi et.al. have already demonstrated an increased production of L-lysine by disrupting *idc* or *cadA* genes encoding lysine decarboxylase in *E. coli*.

Claims 8-9 are drawn to the use of any *Methylophilus* bacterium to produce L-lysine by disrupting lysine decarboxylase gene encoded by SEQ ID NO: 3 or any lysine decarboxylase gene sufficiently homologous to SEQ ID NO: 3 to homologously recombine therewith in view of reducing L-lysine degradation which is an identical concept taught by Kikuchi et al.

Gunji teach methods of how to make mutant *Methylophilus* bacteria from AS1 strain NCIMB10515 in view of enhancing/overproducing L-lysine in *Methylophilus* bacteria. Gunji et. al., teach the efficient production of L-lysine using a methanol assimilating bacterium (*Methylophilus methylotrophus* AS1 strain NCIMB10515) transformed with a mutant LysE gene derived from *Corynebacterium* for efficient recuperation of the L-lysine from the culture medium that contains a one-carbon compound (methanol) as the main carbon source. Gunji et al. stress the benefit of utilizing *Methylophilus* bacteria in producing L-amino acids because methanol is available in large amounts and because of cost effectiveness.

It would therefore have been obvious for a person of ordinary skill in the art to use Kikuchi's method that disrupts the L-lysine decarboxylase gene from *E. coli* to produce a higher levels of L-lysine by disrupting the L-lysine decarboxylase gene in the *Methylophilus* strain of as taught by Gunji et. al. and ferment the culture in a medium that utilizes methanol as the major carbon source which is commercially more advantageous. One of ordinary skill in the art would have been motivated to do so because producing L-lysine from medium containing glucose as taught by Kikuchi et. al would turn out to be more expensive. One of ordinary skill in the art would have a reasonable expectation of success since Kikuchi et.al. demonstrate the increased

products of L-lysine by disrupting lysine decarboxylase in *E. coli* and Gunji et. al WO2000/61723 have demonstrated the use of *Methylophilus* bacterium in producing L-amino-acids from methanol. Therefore claims 7-9 would have been prima facie obvious as stated in the previous Office Action.

Allowable subject matter:

Claims 1-4 and 11 are allowable.

10. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

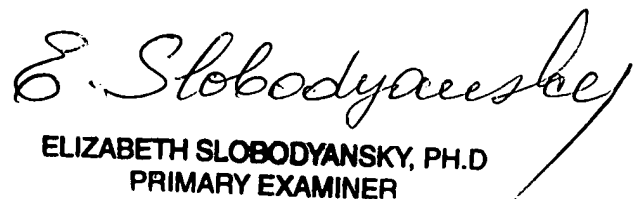
A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice

of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnaw H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
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